

**BIOGRAPHICAL SKETCH**

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NAME: Liu, Zhijie (Jason)

eRA COMMONS USER NAME (credential, e.g., agency login): ZHIJIE\_LIU

POSITION TITLE: Assistant Professor of Molecular Medicine, CPRIT Scholar in Cancer Research

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Lanzhou University, Lanzhou, Gansu, China	B.S.	07/1999	Biochemistry
Chinese Academy of Sciences, Beijing, China	M.S.	07/2002	Molecular Genetics
University of Georgia, Athens, GA	Ph.D.	08/2007	Genetics
University of Georgia, Athens, GA	Postdoctoral	06/2008	Mouse embryonic development
University of California at San Diego, La Jolla, CA	Postdoctoral	01/2016	Transcriptional regulation and cancers

**A. Personal Statement**

My newly established laboratory is focusing on signal-dependent transcriptional programs in cancers, particularly in hormone-related breast and prostate cancers. For over 13 years, I have devoted myself to studying gene expression regulation. My Ph.D. thesis focused on studying signaling and transcriptional regulation in mouse embryonic development. During my postdoc training, I established and utilized powerful inducible *in vivo* labeling approaches to study genome-wide protein-DNA, protein-RNA, and protein-protein interactions of over twenty transcriptional factors, other transcriptional cofactors, and RNA binding proteins. I found that the most active and functionally important estrogen receptor  $\alpha$  (ER $\alpha$ ) enhancers recruited a large number of DNA-binding transcription factors in a combinatorial way through protein-protein interactions. These newly identified ER $\alpha$  'co-activators', termed MegaTrans transcription factors, are required for activation of these ER $\alpha$  enhancers and also serve as a signature of active enhancers. In the past one year, I have well established my own laboratory at UTHSCSA, and my team are embracing my expertise in NGS-based technologies, biochemistry and genetics, and my background in computer science, to study breast and prostate cancers, particularly those resistant to hormone therapy. Our goals are to understand the enhancer activation mechanisms through studying ER $\alpha$ /AR enhancers in hormone-resistant cancers. We hope to provide a solid foundation for identification of new biomarkers and therapeutic targets in treatment of hormone-resistant cancers through investigation of the component/architectural dynamics of ER $\alpha$ /AR-bound enhancers and their high-order interactions with transcription factors and other co-activators (collectively termed the "enhanceosome"). More importantly, the scientific discoveries from this project have the potential to be extended into many other research fields and provide valuable information about treatment paradigms for other diseases.

**B. Positions and Honors****Positions and Employment**

02/2016-current: Assistant Professor, CPRIT Scholar in Cancer Research, Department of Molecular Medicine, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

07/2008-01/2016: Postdoctoral Scholar and Assistant Project Scientist (since 07/2013), The Howard Hughes Medical Institute, Department of Medicine, University of California at San Diego, La Jolla, CA, USA

09/2007-06/2008: Postdoctoral Scholar (to finish my PhD thesis publication), Department of Genetics, University of Georgia, Athens, GA, USA

### **Other Experience and Professional Memberships**

2010-current: Member, American Association for Cancer Research (AACR)

2017-current: Member, American Society for Biochemistry and Molecular Biology (ASBMB)

2014-current: Reviewer and editor (cancer stem cell and gene regulation directions) for *Archives of Stem Cell Research* (<http://www.jscimedcentral.com/StemCell/editors.php>)

08/2015: ad-hoc reviewer for the journal *OncoTargets and Therapy*

09/2015: ad-hoc reviewer for the journal *Epigenetics & Chromatin*

12/2016: ad-hoc reviewer for the grant proposal review for the National Science Centre in Poland

02/2017: ad-hoc reviewer for the journal *Cancer Letters*

### **Awards and Honors**

10/2016: The V Foundation's V Scholar Award for Cancer Research

09/2016: Briscoe Women's Health Scholar Award, School of Medicine, UTHSCSA

07/2016: UT Rising STARs Award

10/2015: CPRIT Award for the Recruitment of First-Time, Tenure-Track Faculty Members

04/2015: 1000 Talent Plan Award, the Chinese Recruitment Program of Global Youth Experts

11/13/2004: The BHSI Retreat Student Poster Award, Biomedical & Health Sciences Institute, University of Georgia, Athens, GA, USA

06/2002: Liu Yongling Scholarship for Excellent Graduate Student, Chinese Academy of Sciences (National-wide award), Beijing, China

06/1999: Graduation with Distinction, Lanzhou University, Lanzhou, China

1995-1999: Undergraduate Scholarship, Lanzhou University, Lanzhou, China

09/1995: Freshmen Scholarship, Lanzhou University, Lanzhou, China

### **Workshops and Courses**

06/06/2013: Application of Computational Biology and High-throughput Sequencing Technologies in Breast Cancer Research, held in Salk Institute, La Jolla, CA, USA

08/06/2006-08/11/2006: Certificated Workshop Training on Human Embryonic Stem Cells: Methods in Human Embryonic Stem Cells, held in Jackson Laboratories, Bar Harbor, Maine, USA

### **Invited Oral Presentations**

09/15/2016: Cancer Development and Progression Research Forum (CTRC, UTHSCSA), *The Dynamics of Enhancer Machinery and Cancer Progression* (Invited Speaker)

06/28/2016: Fujian Provincial Cancer Hospital & Institute (Fujian, China), *Functional Studies of ER $\alpha$ /AR Enhancers in Cancer Hormone Resistance* (Invited Speaker)

06/26/2016: The Fourth Military Medical University (Xi'an, China), The Sixth International Workshop on Cancer Systems Biology (ICSB), *Functional Studies of ER $\alpha$ /AR Enhancers in Breast and Prostate Cancer Biology* (Invited Speaker)

12/01/2014: The National Institutes of Health (Bethesda, MD, USA), The 2014-2015 Genetics and Genomics Stadtman Symposium, *Multi-Level Study of Gene Regulation in Development and Cancer* (Invited Speaker)

11/11/2014: The Sanford Children's Health Research Center (Sioux Falls, SD, USA), Invited talk, *Genome-wide Study of Enhancer Activation Mechanism and Its Implication in Breast Cancer Hormone Resistance* (Invited Speaker)

06/21/2011: The University of California at San Diego (La Jolla, CA, USA), The Cancer and Mammals Meetings supported by Growth Regulation & Oncogenesis Training Grant [NIH/NCI T32 CA009523], *Retinoic Acid Inhibits Breast Cancer Growth by Crosstalk with Other Signals* (Invited Speaker)

05/05/2007: The University of North Carolina-Chapel Hill (Chapel Hill, NC, USA), The 2007 Southeast Regional Meeting of the Society for Developmental Biology, *The regulation of parathyroid hormone expression in thymus by Gcm2-dependent and Gcm2-independent pathways* (Invited Speaker)

## C. Contribution to Science

1. We have uncovered a novel mechanism underlying the interaction of different signaling-dependent transcription factors at enhancers and identify new enhancer co-activators. Previous genome-wide studies indicate that, in addition to the sites with their cognate DNA binding motifs, transcription factors (TFs) also bind to several thousand sites named as 'hotsots' or 'clusters' in a collaborative or combinatorial patterns. Focusing on transcriptional regulation in breast cancer, I found that the most active and functionally important ER $\alpha$  enhancers recruited multiple DNA-binding transcription factors to form a complex through protein-protein interactions. These newly identified ER $\alpha$  'co-activators', termed MegaTrans transcription factors, are required for activation of these ER $\alpha$  enhancers and serve as a signature of active enhancers. My work, published in *Cell*, revealed that ER $\alpha$ , the most critical regulator in breast cancer, recruits *trans*-bound transcription factors upon estrogen signaling to activate its enhancers. The combinational function of different TFs (TF 'hotspots' phenomenon) is also commonly seen in other biological contexts. Our recent studies have shown that RAR and other TFs were also recruited in *trans* to androgen receptor (AR)-bound enhancers and required for AR response to androgen in prostate cancer. Thus, my work has uncovered a basic mechanism of enhancer regulation that might be involved in hormone resistance in cancers.

- a. **Zhijie Liu\***, Daria Merkurjev, Feng Yang, Wenbo Li, et al., and Michael G. Rosenfeld. Enhancer activation requires *trans*-recruitment of a mega transcription factor complex. *Cell*. 2014 Oct 9; 159(2): 358-73. PMID: 25303530 (\*first and co-corresponding author)
- b. **Zhijie Liu\***, Qidong Hu, and Michael G. Rosenfeld. Complexity of the RAR-mediated transcriptional regulatory programs. Chapter 10 of Book "The biochemistry of retinoic acid receptors I: structure, activation, and function at the molecular Level". *Subcellular Biochemistry*. 2014; 70: 203-225. PMID: 24962887 (\*first and co-corresponding author)
- c. Wenbo Li, Yiren Hu, Soohwan Oh, Qi Ma, Daria Merkurjev, Xiaoyuan Song, Xiang Zhou, **Zhijie Liu**, et al., and Michael G. Rosenfeld. Condensin I and II complexes license full estrogen receptor  $\alpha$ -dependent enhancer activation. *Molecular Cell*. 2015 Jul 16; 59(2): 188-202. PMID: 26166704 (Role in this paper: provided technical assistance for different next-gen sequencing experiments including ChIP-seq, 3C, and GRO-seq and their computational analyses)
- d. Janusz Puc, Piotr Kozbial, Wenbo Li, Yuliang Tan, **Zhijie Liu**, Tom Suter, Kenneth A. Ohgi, Jie Zhang, Aneel K. Aggarwal, and Michael G. Rosenfeld. Ligand-dependent enhancer activation requires topoisomerase-I catalytic activity. *Cell*. 2015 Jan 29; 160(3): 367-80. PMID: 25619691 (Role in this paper: generated biotin-TOP1 stable cell line and carried out TOP1 ChIP-seq)

2. We developed and used a powerful inducible *in vivo* biotin labeling approach to study genome-wide protein-DNA, protein-RNA, and protein-protein interactions for over twenty transcriptional factors, cofactors, and RNA binding proteins in many different research projects. This method has been successfully applied in several studies on enhancer components and architectural regulation. Prior to the development of this biotin labeling strategy, we heavily relied on antibodies to perform genome-wide assays including ChIP-seq and CLIP-seq. The biotin tag system I set up has allowed us to perform these assays and obtain high-quality data without relying on antibodies, thereby advancing the field.

- a. Lizhen Chen, **Zhijie Liu**, Bing Zhou, Chaoliang Wei, Yu Zhou, Michael G. Rosenfeld, Xiangdong Fu, Andrew D. Chisholm, and Yishi Jin. CELF RNA binding proteins promote axon regeneration in *C. elegans* and

mammals through alternative splicing of syntaxins. **eLife**. 2016 Jun 2; doi: 10.7554/eLife.16072. PMID: 27253061 (Role in this paper: performed mouse model work and different next-gen sequencing experiments including CLIP-seq and RNA-seq, and conducted integrative next-gen sequencing analyses)

- b. Jianxun Wang, Francesca Telese, Yuliang Tan, Wenbo Li, Chunyu Jin, Xin He, Harihar Basnet, Qi Ma, Daria Merkurjev, Xiaoyan Zhu, **Zhijie Liu**, et al., and Michael G. Rosenfeld. LSD1n is an H4K20 demethylase regulating memory formation via transcriptional elongation control. **Nature Neuroscience**. 2015; 18(9): 1256-1264. PMID: 26214369 (Role in this paper: performed the biochemical characterization of LSD1n including some ChIP-seq experiments)
- c. Feng Zhang, Bogdan Tanasa, Daria Merkurjev, Chijen Lin, Xiaoyuan Song, Wenbo Li, Yuliang Tan, **Zhijie Liu**, et al., and Michael G. Rosenfeld. Enhancer-bound LDB1 regulates a corticotrope promoter pausing repression program. **Proc Natl Acad Sci USA**. 2015 Feb 3; 112(5): 1380-5. PMID: 25605944 (Role in this paper: performed the biochemical characterization of LDB1 including *in vivo* biotinylation, co-immunoprecipitation, and ChIP-seq experiments)
- d. Dorota Skowronska-Krawczyk, Qi Ma, Michal Schwartz, Kathleen Scully, Wenbo Li, **Zhijie Liu**, et al., and Michael G. Rosenfeld. Required interactions of enhancers with Matrin-3 nuclear architecture for transcriptional activation by homeodomain factors. **Nature**. 2014 Aug 3; 514(7521): 257-61. PMID: 25119036 (Role in this paper: performed the biochemical characterization of  $\beta$ -catenin including *in vivo* biotinylation, co-immunoprecipitation, and ChIP-seq experiments)

3. Reveal molecular and cellular mechanisms involved in parathyroid and thymus organogenesis. Using mouse genetic tools and embryonic stem cell technologies, I have identified the role of transcription factor Gcm2 in parathyroid organogenesis from 3<sup>rd</sup> pharyngeal pouch endoderm during mouse embryogenesis. I have also revealed the cellular origins for thymus-associated parathyroid hormone and cervical thymus, challenging previous understandings in the field. My studies have provided important insights in understanding diseases related to the two organs that are very important in endocrine and immune systems.

- a. Kaitlin A. G. Reeh, Kim T. Cardenas, Virginia E. Bain, **Zhijie Liu**, Micheline Laurent, Nancy R. Manley and Ellen R. Richie. Ectopic TBX1 suppresses thymic epithelial cell differentiation and proliferation during thymus organogenesis. **Development**. 2014 Aug; 141(15): 2950-8. PMID: 25053428
- b. Jie Li, **Zhijie Liu**, Shiyun Xiao and Nancy Manley. Transdifferentiation of parathyroid cells into cervical thymi promotes atypical T cell development. **Nature Communications**. 2013 Dec 17; 4:2959. PMID: 24343363
- c. **Zhijie Liu**, Alison Farley, Lizhen Chen, Beth J. Kirby, Christopher S. Kovacs, C. Clare Blackburn, Nancy Manley. Thymus-associated parathyroid hormone has two cellular origins with distinct endocrine and immunological functions. **PLoS Genetics**. 2010 Dec 23; 6(12):e1001251. PMID: 21203493
- d. **Zhijie Liu**, Shannon Yu, Nancy Manley. Gcm2 is required for the differentiation and survival of parathyroid precursor cells in parathyroid/thymus primordia. **Developmental Biology**. 2007 May 1; 305(1): 333-46. PMID: 17382312

#### Complete List of Published Work in MyBibliography:

<http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/50556212/?sort=date&direction=ascending>

## D. Research Support

### ACTIVE

(PI: Liu)

CPRIT

03/01/2016-02/29/2020

Total Research Direct Costs: \$1,900,000

Cancer Prevention and Research Institute of Texas (CPRIT) provided Dr. Jason Liu a First-Time Tenure-Track Faculty Member Award (total \$2,000,000) to support him over 4 years to study the molecular mechanism and identify new biomarkers of breast cancer phenotypic transitions during endocrine therapies.

### ACTIVE

(PI: Liu)

UT Rising STARS Award

07/01/2016-06/30/2019

Total Research Direct Costs: \$250,000

The University of Texas System gave Dr. Jason Liu a Rising STARS award in the amount of \$250,000 for equipment, repair and renovations.

ACTIVE

(PI: Liu)

02/01/2016-01/31/2021

UTHSCSA Start-Up

Total Research Direct Costs: \$687,457

The University of Texas Health Science Center at San Antonio provided Dr. Jason Liu a Start-up fund to set up his lab for cancer research in the Department of Molecular Medicine.

ACTIVE

(PI: Liu)

09/15/2016-09/14/2017

SOM Translational Women's Health Research Program Total Research Direct Costs: \$50,000

The School of Medicine of the University of Texas Health Science Center at San Antonio provided Dr. Jason Liu a Briscoe Women's Health Scholar Award to study the functional mechanism of *trans*-bound transcription factors at estrogen receptor  $\alpha$  enhancers during cancer progression.

ACTIVE

(PI: Liu)

11/01/2016-10/31/2018

V Scholar Award 2.4 Calendar (20.00%)

Total Research Direct Costs: \$200,000

The V Foundation provided Dr. Jason Liu a V Scholar Grant Award for Cancer Research to study the architectural regulation of estrogen receptor  $\alpha$  enhancers in breast cancer.

ACTIVE

(Project Leader: Liu)

03/01/2017-02/28/2022

1 U54 CA217297-01 1.8 Calendar (15.00%)

Total Direct Research Costs: \$7,115,521

We have applied for the National Cancer Institute (NCI) Special Emphasis Panel Research Centers for Cancer Systems Biology Consortium (U54) RFA-CA-15-014. This U54 fund to our center has been just approved. We will focus on studying "Systems Analysis of Epigenomic Architecture in Cancer Progression".

PENDING

(PI: Liu)

07/01/2017-06/30/2022

1 R35 GM124592-01

Total Direct Research Costs: \$1,250,000

This is Maximizing Investigators' Research Award for Early Stage Investigators (R35) supported by the National Institute of General Medical Sciences (NIGMS).

High-order assembly and 3D architectural regulation of enhancer activation machinery

## **Summary of the project that Xiangya students would be participating in Dr. Jason Liu's Lab**

### **Functional studies of a newly identified category of ER $\alpha$ 'co-activators' in breast cancer hormone resistance**

The objective of our study is to find better ways to prevent, diagnose, and treat hormone-resistant breast cancers. A long-standing challenge in treating breast cancer is why certain patients with cancers expressing estrogen receptor- $\alpha$  (ER $\alpha$ ) do not benefit from hormonal therapies targeting ER $\alpha$ . Despite intensive studies over the past decades, molecular mechanisms underlying hormone resistance remain unclear. ER $\alpha$ -controlled DNA regulatory elements, especially enhancers, play very important roles in gene regulation to promote the growth and proliferation of breast cancer cells. Exploring the fundamental regulation mechanism of enhancer chromosomal organization would provide transformative increments in understanding of ER $\alpha$ -mediated transcriptional programs, and help predict or even overcome the refractory stage of endocrine therapies.

Using integrative omics approaches, we have recently uncovered a group of novel ER $\alpha$ -mediated enhancers that exhibit estrogen-dependent activation in the initial stage but later develop ligand-independent "autonomy" during advanced progression. We also revealed a group of trans-bound transcription factors (MegaTrans TFs) that may function as a new category of ER $\alpha$  'co-activators' to maintain the constitutive activation of ER $\alpha$  enhancers. We hypothesize that MegaTrans TFs play critical roles in both E<sub>2</sub>-dependent and E<sub>2</sub>-independent ER $\alpha$  enhancer activation events during the assembly of a functional machinery that activates specific transcriptional regulatory programs in breast cancer, and that in accordance with their specific functions, these newly identified 'co-activators' might be biomarkers for therapeutic intervention of hormone-resistant cancers. To test these hypotheses, we propose the following Specific Aims:

#### **Specific Aim 1: Test whether trans-bound MegaTrans TFs are correlated with hormone resistance.**

Over-activation of RAR $\alpha$  and AP1 has been observed in hormone-resistant breast cancers. Both RAR $\alpha$  and AP1 are components in MegaTrans complex. Given the critical roles of MegaTrans complex in activating ER $\alpha$  enhancers and the enhancer function in controlling cancer gene expression, we plan to test whether the composition and/or expression levels of MegaTrans complex are altered in hormone-resistant breast cancers, and whether MegaTrans TFs can serve as biomarkers for hormone resistance.

#### **Specific Aim 2: Test whether MegaTrans TFs activate ER enhancers and promote cancer growth under antiestrogen treatment.**

After testing the correlation, we will test whether overexpression of MegaTrans TFs is sufficient to activate ER enhancers in the absence of E<sub>2</sub> or in the presence of ER antagonist tamoxifen. Enhancer activity will be examined by GRO-seq to check genome-wide enhancer RNAs (eRNAs) profile.

#### **Specific Aim 3: Determine the interaction of MegaTrans complex.**

We have previously shown that MegaTrans TFs are recruited to ER $\alpha$  enhancers through protein-protein interaction, but how do they interact with each other remains unknown. In this aim we will dissect the interaction hierarchy and the domains mediating the interaction, which will provide important insights for selecting therapeutic targets.

The Xiangya student will be participating in the project under my direct supervision. With the sufficient funding support from my CPRIT, UT Rising STARs, V Scholar, and recently funded NIH U54 Center grant, this Xiangya student will have a lot of chances to touch the cutting-edge research. Our ultimate goal is to provide a solid foundation for identification of new biomarkers and therapeutic targets through investigation of the working mechanism and functional contribution of ER $\alpha$  enhancers and their high-order interactions with transcription factor complexes (collectively termed enhanceosome) in treatment of hormone-resistant breast cancers. This project will build a basis for extended mechanistic studies and drug screens targeting ER $\alpha$  enhancers. We expect to publish at least one paper with the Xiangya student as the first author before this Xiangya student graduates.